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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/836,576	Applicant(s) Haensler et al.
	Examiner Brenda Brumback	Group Art Unit 1643

☒ Responsive to communication(s) filed on *Aug 31, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *25-86* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *25-86* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The examiner acknowledges receipt of the Supplemental Information Disclosure Statement filed March 4, 1998 and the Preliminary Amendment filed August 31, 1998 canceling claims 1-24 and adding new claims 25-86. Pending claims are 25-86.

Specification

2. The objection to the specification for lacking continuation data for the International Application PCT\FR95\01495 is withdrawn pursuant to applicant's amendment of August 31, 1998, adding the data.

Claim Objections

3. The objection to Claims 1-24 as lacking proper introduction is withdrawn due to applicant's amendment of August 31, 1998, adding an introduction.

4. Claims 50-61 are objected to under 37 CFR 1.75(c), as being of improper dependent form because they are substantial duplicates of claims 25-36, from which they ultimately depend, and also as being of improper dependent form because they ultimately depend from themselves. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Double Patenting

4. Claims 25-86 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-49 of copending Application No. 08/903,978. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same amphipathic compounds and their use as adjuvants in vaccines.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The rejection of claims 1-14 under 35 U.S.C. 112, second paragraph, and under 35 U.S.C. 101 are withdrawn subsequent to applicant's cancellation of claims 1-14 and rewriting of the claims to recite active method steps.

6. Claim 65 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a TH1 response in mice, does not reasonably provide enablement for this response in any mammal, including a human. The specification (Example 12, pages 16-17) teaches a large increase in IgG2a in mice as indicative of stimulation of TH1 lymphocytes. The art teaches that TH1 lymphocytes are associated with generation of IgG2a antibodies in mice, but

that the equivalent human subclasses are unknown (see Couper et al., Database SciSearch on Dialog, No. 06948805, Human Immunology, 1998, V59, N8, pp. 493-499, 1998). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with this claim.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 25-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolcsak et al. (U.S. Patent 5,100,662) in view of Gao et al. (Biochemical and Biophysical Research Communications, 179:280-285, 1991), both references of record.

Bolcsak et al. teach immunogenic compositions comprising an antigen entrapped within a vesicle or liposome, which comprises a sterol linked to a charged group (column 5, lines 5-41). Bolcsak et al. teach one sterol embodiment as derivatized cholesterol (column 6, lines 51-54 and column 11, lines 37-38) and teach a preferred embodiment of the immunizing antigen as influenza virus hemagglutinin (column 6, lines 26-38). Bolcsak et al. also teach an embodiment comprising the derivatized sterol in combination with another lipid, such as DMPC (column 6, lines 45-65).

Bolcsak et al. teach that the vesicles or liposomes with entrapped immunogen and adjuvant are stable for long periods of storage (column 5, lines 42-47) and are readily endocytosed by cells (column 6, lines 21-22). Bolcsak et al. teach administration of the vaccine composition either simultaneously or separately over time (column 8, lines 3-19) by any suitable route, including mucosal, subcutaneous, and nasal (column 15, lines 24-31). The claimed invention differs from the composition disclosed by Bolcsak et al. in the specific recitation of dioleoylphosphatidyethanolamine or dioleoylphosphatidylcholine as the neutral lipid used and also in the recitation of a carbamoyl linkage of the sterol and the charged group. Bolcsak et al. teach that the core sterol molecule can be attached to the charged group via a number of different bridges, such as an ester bond, for example (column 5, lines 22-26), and teach that the chemical linkage should be chosen to promote the stability of the liposomes during long periods of storage (column 11, lines 56-64).

Gao et al. teach that liposomes prepared from the cationic derivative of cholesterol, 3β[N-(N', N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Chol) and dioleoylphosphatidylethanolamine (DOPE) efficiently transfect mammalian cells with significantly less toxicity than other liposomal preparations. Gao et al. also teach that synthesis of DC-Chol is a simple one-step procedure and that small liposomes of DC-Chol and DOPE are easily prepared (see pages 280-281, Abstract and first paragraph, and page 282, paragraph 1, under *Results and Discussion*). Finally, Gao et al. teach that DC-Chol, containing a carbamoyl bond, is much more

stable than similar amphiphiles with an ester bond (page 284, last 2 lines), while still being biodegradable once they are inside cells (page 285, lines 5-7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the liposome composition taught by Gao et al. in the vaccine preparations taught by Bolcsak et al. in order to improve endocytosis, prolong shelf-life, and reduce toxicity of the immunogenic composition, because these characteristics are as desirable for vaccine adjuvants as they are for transfection compositions.

b. Claims 25-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popescu et al. (EPA 0 356 339) in view of Epand et al. (U.S. Patent 5,283,185).

Popescu et al. teach vaccine compositions comprising influenza virus hemagglutinin and liposome adjuvants of dimyristolyphosphatidylcholine (DMPC)/cholesterol (see the abstract and page 2, paragraph 1) and teach producing an immune response by administering the vaccine composition by a suitable route, such as subcutaneous or oral, among others (page 9, last full paragraph). Popescu et al. teach the immune response as humoral or cell-mediated. Popescu et al. teach administering the antigen and adjuvant either simultaneously or separately over time (page 4, line 62, through page 5, line 15).

Epand et al. teach that some cationic amphiphiles are known to facilitate the transfer of DNA into cells, probably through enhanced binding of the DNA-lipid complex to the cell surface via the excess positive charges on the complex (column 1, lines 8-17). Epand et al. teach a

method for facilitating the transfer of nucleic acids into cells with a stable aqueous dispersion comprising the nucleic acid and a dispersion of mixed lipids comprising a lipophilic group derived from cholesterol, a linker bond of a carboxyamide or carbamoyl, a spacer arm of an alkyl chain, and a cationic amino group; and a co-lipid of phosphatidylcholine or phosphatidylethanolamine. Epand et al. teach the cationic lipid as selected from the group consisting of cholesteryl-3β-carboxamidoethylenetrimethylammonium iodide, cholesteryl-3β-carboxamidoethyleneamine, cholesteryl-3β-oxysuccinamidoethylenetrimethylammonium iodide, 3β-{N-(N',N'-dimethylaminoethane)-carbamoyl]-cholesterol, and 3β-{N-(polyethyleneimine) carbamoyl]-cholesterol (column 14, lines 51-68; column 15, lines 16-27; and column 16, lines 1-26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the mixed-lipid composition taught by Epand et al. in the vaccine composition of Popescu et al. for an improved adjuvant which would enhance the immune response of the target cells to the immunizing antigen by facilitating cell surface and antigen/lipid interaction.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Marian Knode whose telephone number is (703) 308-4311. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone

number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1643 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1643 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
September 23, 1998

SONIA WORTMAN
PATENT EXAMINER